Pneumococcal Disease (Childhood)

In this segment of our program we will discuss pneumococcal disease of childhood. Until recently, we did not have much to say on this topic because there was nothing to prevent it. That all changed in 2000, when the world's first conjugate pneumococcal vaccine was licensed. The pneumococcal chapter begins on page 233 of the text if you want to follow along.

Streptococcus pneumoniae, or pneumococcus, was first isolated by Louis Pasteur in 1881. The chemical structure and role of pneumococcal capsular polysaccharide was worked out by 1945. The first attempts at a vaccine began as early as 1911. *Streptococcus pneumoniae* are **gram positive bacteria**. There are **90 known serotypes**. As with other encapsulated organisms, the **polysaccharide capsule is an important virulence factor, and capsular type specific antibody is protective**.

Although all serotypes may cause serious disease, a relatively limited number of serotypes cause the majority of invasive infections. Overall, the 10 most common serotypes are estimated to account for about 60 percent of invasive disease worldwide. But the ranking and serotype prevalence differs by age group and by geographic area. Among children less than 6 years of age in the U.S., seven serotypes account for 80% of isolates from blood or cerebrospinal fluid. In contrast, these same 7 serotypes account for only about 50% of isolates from older children and adults.

Pneumococcus is a frequent inhabitant of the upper respiratory tract and may be isolated from the nose, throat, or both of about 10% of people at any given time. Carriage rates among children may be even higher. Nearly all people carry pneumococci at some time during the course of a year. We do not understand why some of these people go on to develop invasive disease. Host factors, like underlying illness, are probably important. But people without any underlying illness may also develop invasive pneumococcal disease.

Bacteremia without a known site of infection is the most common invasive clinical presentation in children less than 2 years of age. Bacteremia accounts for about 70% of invasive disease in this age group. With the decline of invasive Hib disease, pneumococcus has become the **most common cause of bacterial meningitis among children less than 5 years of age** in the United States. **The highest rates of meningitis are among children less than 1 year of age**, approximately 10 cases per 100,000 population.

The burden of pneumococcal disease among children less than 5 years of age is significant. In the prevaccination era, an estimated **17,000 cases of invasive**

disease occurred each year. **13,000 of these were bacteremia without a known site of infection** and about **700 were cases of meningitis**. An estimated **200 children died** every year as a result of invasive pneumococcal disease. Although not considered invasive disease, it was estimated that **5 million cases of acute otitis media occurred each year** among children less than 5 years of age. By one year of age more than 60 percent of children had at least one episode of acute otitis media. Middle ear infections are the most frequent reason for pediatric office visits in the United States and result in more than 20 million visits annually. Otitis media is also the leading reason for prescribing antibiotics during childhood.

Pneumococci are also an important cause of pneumonia in children. In two prospective studies, 17% to 28% of community-acquired pneumonia were diagnosed as pneumococcal. This translates into tens of thousands of cases each year.

Pneumococcus is a human pathogen that occurs throughout the world. The **reservoir of pneumococci is believed to be the nasopharynx of human carriers**. As I mentioned earlier, up to 10% of people are colonized with pneumococci at any given moment. Transmission probably occurs mostly from asymptomatic carriers by **respiratory droplets**. For this reason, a vaccine that could reduce nasopharyngeal carriage could indirectly protect unvaccinated contacts. The communicability of pneumococci is not known with certainty, but **transmission can probably occur as long as the organism is present in respiratory secretions**.

Much of our knowledge of the incidence and risk factors for invasive pneumococcal disease comes from special studies and surveillance systems. One such special surveillance system is CDC's Active Bacterial Core Surveillance -- known as ABCs. This graph shows the incidence of invasive pneumococcal disease by age group in **1998**, based on data from the ABCs. The vertical axis shows incidence, expressed as rates per 100,000 population. The horizontal axis shows age groups. The highest rates are in children less than 2 years. Incidence falls to its lowest point among children 5 to 17 years of age. The incidence of pneumococcal disease then rises steadily with increasing age. But the incidence of invasive pneumococcal infection in persons 65 and older is less than half that in young children. Although pneumococcal infections occur in healthy children, there are medical and other factors that increase the risk significantly. Children with **functional or anatomic asplenia**, **sickle cell disease and other sickle hemoglobinopathies**, and **children with HIV infection** are at extremely high risk of invasive disease. Some studies estimate rates more than 50 times higher than children of the same age without these conditions. **Recipients of a cochlear implant** are a group recently recognized to be at increased risk for invasive pneumococcal disease. A cochlear implant is an electronic device utilized by people with profound hearing loss that cannot be corrected by hearing aids. There are estimated to be about 25,000 recipients of these devices in the United States. Since 2002, FDA and CDC have been investigating reports of meningitis among recipients of these implants. More than

50 cases of meningitis have been reported in individuals who have had cochlear implants. Two-thirds of these infections were in young children. The reason why the implants appear to predispose the recipient to meningitis is not known. **Out of home group child care** has been shown to increase the risk of invasive pneumococcal disease and acute otitis media. The risk for children in these settings is increased 2 to 3 fold among children less than 5 years of age. Finally, children of certain racial and ethnic groups have increased rates of invasive pneumococcal disease. These include **Alaskan Natives, certain American Indian groups, and African Americans**. The rate of invasive disease for these children are 3 to 4 times higher than for other healthy children at every age. The reason for this increased risk is not clear. Socioeconomic factors may account for some of this increased risk. But some studies have reported increased risk even when controlling for income. Data collected by the Active Bacterial Core Surveillance system suggests that the conjugate vaccine is already having an impact on invasive pneumococcal disease in young children. We asked Doctor Cynthia Whitney, a medical epidemiologist in the CDC National Center for Infectious Diseases, to tell us about this exciting trend.

Since 1995, the Emerging Infections Network Program and CDC have conducted active surveillance for invasive disease caused by *Streptococcus pneumoniae* and other bacteria. The surveillance system is called Active Bacterial Core Surveillance- known as ABCs.

ABCs has sites in 10 states, and includes a population of more than 20 million persons. It is an active, population based, laboratory based system. In each site, surveillance personnel contact laboratories to identify cases and collect isolates. Data are aggregated and analyzed at CDC.

The first pneumococcal conjugate vaccine was licensed in the United States in February 2000. The Advisory Committee on Immunization Practices and the American Academies of Pediatrics and Family Physicians recommended the vaccine for all children younger than 2 years of age in October 2000. Despite widespread vaccine shortages that began in 2001 and persisted into early 2003, ABCs data suggest that the conjugate vaccine is already having an impact on invasive pneumococcal disease.

This graphic shows the incidence of invasive pneumococcal disease among children less than 5 years of age in 1 year increments, from 1998 through 2002. 1998 and 1999 are considered the baseline years, before licensure of conjugate vaccine. In 1998 and 1999 the highest incidence rates were among children one year of age - about 210 cases per 100,000 population, and among children younger than 1 year of age - about 170 per 100,000 population. Rates among 2, 3, and 4 year old children were lower than among younger children, but still above the overall national rate of about 23 cases per 100 thousand population.

Notice the decline that occurred starting in 2000, the year the conjugate vaccine was licensed. By 2002, the rate of invasive pneumococcal disease among children younger than 2 years of age- shown here by the red and yellow lines- was about 34 cases per 100,000 population. This represents a decline in

incidence of approximately 75% compared to the baseline rate. Disease among 2 years olds dropped by 72% by 2002. The rates of disease in 3 and 4 year-old children have also fallen, but less than rates among younger children. However, recall that pneumococcal conjugate vaccine is not routinely recommended for children older than 2 years of age.

Vaccinating children may also be beneficial for adults. Studies suggest that transmission from children may be responsible for a fair amount of pneumococcal disease in adults. For example, adults living with young children have higher rates of nasopharyngeal carriage and higher risk of pneumococcal disease than those without a young child in the household. Available evidence also suggests that pneumococcal conjugate vaccine reduces nasopharyngeal carriage of pneumococcal strains contained in the vaccine, and so should indirectly reduce carriage and disease rates in close contacts of vaccinated children. ABCs data suggests that this is occurring.

Here we see the incidence of invasive pneumococcal disease among adult age groups from 1998 through 2002. The incidence of disease has declined in all age groups compared to the baseline in 1998 and 1999. Among adults, the highest rates of disease are in those 65 years and older. This group also accounts for most deaths from pneumococcal disease in the US. In this age group, rates have fallen from about 60 cases per 100,000 population to about 43 cases per 100,000 population – a 29% reduction. An even larger decline has been seen among 20 to 39 year olds -- shown here by the green line – whose rate has fallen 46% compared to baseline. This most likely represents reduced transmission of pneumococcus from children to their parents.

We believe that the decline in rates of disease I've described is a result of the use of pneumococcal conjugate vaccine. Historically, rates of invasive pneumococcal disease have varied somewhat from year to year. However, changes of the magnitude we've seen in the last few years are not what we would expect to see with this type of variation. Similarly, while use of pneumococcal polysaccharide vaccine has increased in the last few years, the increase in use isn't enough to account for what we are seeing. While these changes are very exciting, it's only the start to the story. We don't yet know how far disease will drop or if other pneumococcal strains will start to fill in the gaps created by the pneumococcal conjugate vaccine. We will continue to monitor the ABCs data closely to see what happens.

The first attempts at producing a pneumococcal vaccine began about the time of the First World War. It would be almost 70 years before the first pneumococcal vaccine was licensed in 1977. This vaccine contained polysaccharide from 14 serotypes of pneumococcus. In 1983 a 23-valent polysaccharide vaccine was licensed, which replaced the earlier vaccine. The problem with polysaccharide vaccines is that they are not effective in young children. Basically, polysaccharide is a T cell independent antigen and does not establish good immunologic memory. Polysaccharide vaccines are generally not effective among children less than 2 years of age, and subsequent doses do not produce a substantial boost in antibody level. Efforts have been underway for years to develop a

pneumococcal CONJUGATE vaccine, analogous to Hib conjugate vaccine, that would protect young children. The first pneumococcal conjugate vaccine was approved by FDA in February 2000. It is called Prevnar, and is produced by Wyeth Vaccines. The vaccine contains purified **pneumococcal polysaccharide conjugated to a nontoxic variant of diphtheria toxin** known as CRM197. It **contains the polysaccharide of 7 serotypes of pneumococci**. The official designation of this vaccine is PCV7: PCV for pneumococcal conjugate vaccine, and 7 for 7-valent. On the immunization schedule it is listed only as PCV. The 7 serotypes included in PCV account for 86% of bacteremia and 83% of meningitis among children younger than 6 years of age. Additional pneumococcal conjugate vaccines containing 9 and 11 serotypes are being developed.

Pure polysaccharide vaccine does not generate a significant immune response in young children. Conjugating the polysaccharide to a protein overcomes this problem. PCV is very effective in children. The efficacy trial included almost 38,000 children in the Northern California Kaiser Permanente system. The vaccine was **97% effective against invasive disease** caused by vaccine serotypes. It was **73% effective against clinically diagnosed pneumonia** in children with x-ray evidence of an area of consolidation. Vaccinated children also had a significant reduction in visits for acute otitis media. Overall there was a **7% reduction in all episodes of acute otitis media**. Frequent otitis media was reduced by 9% to 23%, depending on the definition of frequent. And vaccinated children had 20% fewer tympanostomy tubes placed than unvaccinated children. A 7% reduction in acute otitis media does not sound like very much. An individual child is not likely to experience a noticeable reduction in disease incidence. But remember that there are millions of cases of otitis media every year. A 7% reduction in THIS burden could mean thousands fewer office visits and thousands fewer prescriptions for antibiotics. And THAT is definitely a good thing.

Another benefit of PCV may be its effect on nasopharyngeal carriage of pneumococci. This is important, because if carriage could be reduced, it would indirectly protect unvaccinated contacts of vaccinated children. Several studies indicate that conjugate vaccines reduce nasopharyngeal carriage of vaccine-type pneumococci by about one half. Some but not all studies have found that carriage of pneumococcal serotypes NOT included in the vaccine is higher among vaccinated children. Additional studies of the effect of vaccination on carriage are underway now.

The routine vaccination schedule for PCV is **3 primary doses at 2, 4, and 6 months, with a booster dose at 12 to 15 months**. We will discuss how to modify this routine schedule in the face of a vaccine shortage in a moment. The **first dose may be given as early as 6 weeks of age**. If an accelerated schedule is needed, the **minimum interval between the first three doses is four weeks**. **At least 8 weeks should separate the third and fourth doses**. Children who begin the series of PCV after 7 months of age will need fewer doses than children who begin the schedule at 2 months of age. In this way the vaccine is similar to Hib conjugate vaccine. This table shows the recommended number of doses for children who start the vaccination series late at 7 months of

age and older. Children who receive their first dose at **7 to 11 months** will receive 2 doses separated by at least 4 weeks, and a booster dose 2 months after the second dose. Children beginning the series at **12 to 23 months** of age should receive 2 doses separated by at least 8 weeks with no booster dose. Healthy unvaccinated children **24 to 59 months** of age need only one dose. Children 24 to 59 months of age at high risk of invasive pneumococcal disease – such as those with HIV infection or asplenia – should receive a total of **2 doses** separated by 8 weeks.

You will encounter children who began the PCV series on time but have since fallen behind schedule. If the child is more than one month behind schedule, you will need to use the catch-up schedule to determine how many doses the child needs. The catch-up schedule was published with the routine childhood schedule in January 2004. It is also in Appendix A of your book. It will assist you in determining how many more doses the child needs and when they should be administered. Remember that similar to Hib vaccine, older children may require fewer total doses if they have a lapse in the series or start late.

The American Academy of Pediatrics and ACIP published recommendations on the use of pneumococcal conjugate vaccine in 2000. Both groups agree on how the vaccine should be used. Both AAP and ACIP recommend routine vaccination with PCV for **all children less than 24 months of age**. The vaccine should be integrated into the routine schedule and administered during the same visits as other routine childhood immunizations. Routine vaccination is also recommended for **children 24 to 59 months of age with high risk medical conditions**. These high risk conditions include **functional or anatomic asplenia**, **sickle cell disease** and other sickle hemoglobinopathies, **HIV infection**, **immunocompromising conditions**, a **cochlear implant**, and **chronic illnesses**, such as heart or lung disease, chronic renal failure and nephrotic syndrome. Asthma alone is not considered a high risk condition unless the child is receiving high dose steroid therapy or has obstructive lung disease. Children 24 to 59 months of age with high risk medical conditions should receive 2 doses of pneumococcal conjugate vaccine separated by 8 weeks. These children will also be candidates for pneumococcal polysaccharide vaccine. We will discuss this in more detail in a moment.

Other children could also benefit from vaccination with pneumococcal conjugate vaccine. ACIP recommends that providers **consider vaccination of all other children 24 to 59 months of age**. ACIP recommends that priority be given to vaccination of **children 24 to 35 months of age**, **children of Alaskan native, American Indian, and African American descent**, and **children who attend out of home group child care**. ACIP defines out of home group child care as a setting outside the home where a child regularly spends 4 or more hours per week with 2 or more unrelated children supervised by an adult.

ACIP currently recommends vaccination with PCV only for children 2 to 59 months of age. The vaccine is not routinely recommended for older children and adults, who are candidates for pneumococcal polysaccharide vaccine. In

November 2003 the National Immunization Program was informed of production constraints by Wyeth Vaccines. These production constraints could cause delays in shipment of the vaccine in 2004 through mid-summer, and possibly later. CDC is working closely with the manufacturer to equitably allocate the limited supply of vaccine to all providers. CDC, in consultation with ACIP and the American Academies of Pediatrics and Family Physicians has issued recommendations that are intended to conserve vaccine and minimize the likelihood of a shortage. These recommendations were published in MMWR on February 13, 2004. Until adequate supplies of PCV are available, ACIP recommends that health care providers should **continue to vaccinate high risk children 5 years of age or younger as originally recommended**. We discussed these high-risk medical conditions earlier in the program. However, providers should **temporarily suspend routine use of the fourth dose of PCV among healthy children**.

CDC estimates that this single intervention will help conserve more than 1 million doses by July 2004, making widespread or prolonged disruptions less likely. Data are available which show that healthy children vaccinated on schedule with three doses of PCV during the first year of life are well protected against invasive disease caused by vaccine strains, at least in the short term. I will reiterate that at this time providers should only defer the FOURTH dose in healthy children. Children who start the schedule at seven months of age or later, or who have had a significant lapse in the schedule, should receive all the doses recommended in the late start or catch-up schedules, to a maximum of three doses. Pneumococcal polysaccharide vaccine is not licensed or recommended for children less than 2 years of age. **Do NOT substitute pneumococcal polysaccharide vaccine for PCV in children less than 2 years of age**. Healthcare providers should **maintain a list of children for whom PCV has been deferred**. These children should be **recalled and given their fourth dose when supplies are adequate**.

We have received reports from practices that are experiencing more severe shortages of PCV. In some cases practices report they do not have sufficient vaccine to provide even two doses to children in their practices. If you have a serious shortage of vaccine and are in the public sector, you should contact your state immunization program to obtain additional supplies. If you are in private practice, you should contact Wyeth and request additional vaccine for your practice. There has been no change in the recommendations for pneumococcal polysaccharide vaccine. But there are some situations in which high-risk children two years of age and older could benefit from vaccination with both pneumococcal conjugate vaccine and pneumococcal polysaccharide vaccine. Some children 24 to 59 months of age with high risk medical conditions- such as HIV infection or sickle cell disease- may have already received pneumococcal polysaccharide vaccine. The polysaccharide vaccine has the advantage of containing a larger number of serotypes of pneumococci. But the conjugate vaccine has the advantage of better immunologic priming and induction of immune memory.

ACIP recommends administration of pneumococcal conjugate vaccine to **children at high risk of invasive pneumococcal disease** who have already received pneumococcal polysaccharide vaccine. These children should receive two doses of PCV. The **2 doses** of pneumococcal conjugate vaccine should be separated by 8 weeks, and should be given **at least 8 weeks after the last pneumococcal polysaccharide dose**. Similarly, children who complete the pneumococcal CONJUGATE series before 2 years of age, and who are at high risk of invasive pneumococcal disease, should receive pneumococcal POLYSACCHARIDE vaccine. These children will benefit from the larger number of pneumococcal serotypes contained in the polysaccharide vaccine. ACIP **recommends that children at high risk of invasive pneumococcal disease** receive pneumococcal polysaccharide vaccine. These children should receive **one dose at 2 years of age**, at least **8 weeks after the last dose of pneumococcal conjugate vaccine**. Children at highest risk, such as those with HIV infection or asplenia, will also receive a second dose of pneumococcal polysaccharide vaccine 3 to 5 years after the first dose. This may seem complicated at first. But the recommendations for use of pneumococcal polysaccharide vaccine in high risk children have not changed. Pneumococcal conjugate vaccine is just being added to the schedule for children less than 59 months of age.

Adverse reactions following pneumococcal vaccines are similar to other inactivated vaccines. In the clinical trials, **local reactions** such as redness, swelling or tenderness were reported in 10 to 23 percent of recipients, depending on the dose. In 3 to 4 percent pain was severe enough to interfere with limb movement. **Temperature greater than 38^{o}** centigrade within 48 hours was reported in 15% to 24% of recipients. But in these studies, PCV was often administered simultaneously with whole cell pertussis vaccine. Many of these febrile episodes may have been attributable to the whole cell pertussis vaccine, not the pneumococcal conjugate vaccine. In another study in which ACELLULAR pertussis vaccine was given simultaneously with PCV, 11% of recipients had temperatures of 38^{o} centigrade or higher. **Serious adverse reactions** have not been attributed to the vaccine. Obviously, careful surveillance for less common adverse events will be conducted as more doses of PCV are administered.

Contraindications and precautions for pneumococcal conjugate vaccine are similar to other inactivated vaccines, and for pneumococcal polysaccharide vaccine. A history of a **severe allergic reaction to a vaccine component or following a prior dose** is a contraindication to vaccination. **Moderate or severe acute illness** is a precaution, and vaccination should be delayed until the acute illness improves.

We have one final issue with pneumococcal conjugate vaccine. Since PCV was licensed for use, there have been reports of invasive pneumococcal disease among infants and children who had received at least one dose of the vaccine. But cases of invasive disease following vaccination are to be expected. In the clinical trials that led to licensure, vaccine efficacy was estimated to be 97% for invasive disease with pneumococcal serotypes included in the vaccine, and 89% for all serotypes. The reason that some vaccinated children appear not to be

protected, particularly when the infection is caused by a serotype included in the vaccine, is not known. It is important that we understand more about why some children fail to be protected following vaccination with PCV. We need your help to accomplish this. CDC's Respiratory Diseases Branch, in the National Center for Infectious Diseases, has developed a system to monitor and investigate this and other pneumococcal conjugate vaccine issues. The system is intended to **determine the serotype of these invasive pneumococcal isolates**, **determine conditions in the child that may increase the risk of severe pneumococcal disease**, and **monitor for vaccine lots that may be less effective**.

There are four conditions that must be met in order for a case to be eligible for reporting. First, **the child is less than 5 years old**. Second, the child has an **invasive pneumococcal infection**. An invasive infection is defined as isolation of *Streptococcus pneumoniae* from a normally sterile site, such as cerebrospinal fluid, blood, joint fluid, or pericardial fluid. Third, there is a **pneumococcal isolate available for serotyping**. And, the fourth condition is the **child has a history of at least one dose of PCV**. If all four conditions are met, a PCV failure **case report form should be completed and sent along with the isolate and a CDC lab report form to your State Health Department**. It is important to fill out the case report form as completely as possible, including the vaccination history. Your **State Health Department will send the isolate, case report form, and laboratory form to the Streptococcus laboratory at CDC**. Cases of suspected PCV failure **may also be reported to the Vaccine Adverse Events Reporting System, or VAERS**. Reporting to VAERS about these cases is not required unless there is a clinically significant adverse event after vaccination with PCV. The **PCV Failure Case Report** and an instruction sheet are available on the NIP website. The instruction sheet will provide information on how to complete the case report and send the isolate. We will include these websites on the resource page for this broadcast.

A new era has begun in the prevention of invasive pneumococcal disease in children. It is likely that additional vaccines with even more serotypes will be licensed in the future. Hopefully, the incidence of pneumococcal disease in infants will continue to fall and the disease will become a rarity, the same way Hib conjugate vaccine has made Hib disease a rarity.

Q: Many offices are now stocking both pneumococcal conjugate AND polysaccharide. Any concerns about administration errors?

A: Yes, having two types of pneumococcal vaccine in the same refrigerator does increase the risk of a vaccine administration error. We have already heard of several instances in which polysaccharide vaccine was given to an infant, and conjugate vaccine was given to an older child or adult. Pneumococcal polysaccharide is not recommended for children less than 2 years of age because it is not effective in this age group. Conjugate vaccine is not recommended for people older than 5 years of age. The larger number of serotypes in the polysaccharide vaccine is advantageous to older people. Providers ALWAYS need to verify the correct vaccine is being given before

injecting it. We all want to avoid administration errors. If a child is inadvertently given a dose of polysaccharide vaccine you should administer the correct vaccine as soon as the error is discovered. If an adult receives conjugate vaccine, ACIP recommends waiting 2 months before giving the polysaccharide vaccine.